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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,140	06/16/2005	Peter Bernstein	133087.02301(100945-1PUS)	9263

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EXAMINER	
O'DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,140	BERNSTEIN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10 and 12-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10 and 12-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7, 10, 12-23 are pending in the current application.

2. This application is a 371 of PCT/SE03/02004 filed 12/18/2003 which claims benefit of 60/435,130 filed 12/20/2002.

Response to Arguments

3. Applicant's arguments filed December 19, 2007 have been fully considered but they are not fully persuasive. The rejections of claims 8, 9 & 11 are withdrawn since they have in fact been canceled. The rejection under 35 U.S.C. 103 (a) for obviousness is maintained. The applicant has argued that Stevenson has some deficiencies with regard to the teaching of naphthyl. The examiner disagrees, as one of ordinary skill would recognize the lipophilicity of naphthyl as being similar to the bis-trifluoromethylphenyl. In response to the applicant's teaching of the negative influence of sterics, the examiner disagrees with the characterization of naphthyl as sterically bulky as compared to the phenyl. In fact naphthyl is not really that different in effective steric bulk from bis-trifluoromethylphenyl. Regardless, in order to buttress the examiner's conclusion and show that the examiner is not taking official notice, the examiner submits that Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773, clearly teaches the exact modification (down to the very precise substituents on the naphthyl ring), thus the use of naphthyl in these NK1-antagonists and the substitution of naphthyl for phenyl was very well known even in this very small field. Starting with the known selective antagonist SR48968, Bernstein modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with "over 100 aryl, heteroaryl and arylalkyl groups". In the words of

Bernstein the result of this study was "the most potent, dual acting compound to come out of this array was the naphthamide **2a**". Bernstein goes on to describe that "to follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring." It is interesting that 3-cyano-naphthyl was the preferred substituent, as in compound **4**. This 3-cyano naphthyl group is also the preferred substituent of the instant case and is what distinguishes these compounds from those of Stevenson et. al. There can be no doubt that this was the preferred substituent.

The examiner maintains the 112 1st paragraph rejections for enablement, since the assays presented (ligand binging assays) do not correlate with disease treatment. The applicant has argued in terms of the success of certain clinical trials with other compounds, however the key issue here is the correlation between the assay presented and treatment of a disease. No such correlation exists. The real problem here is that the NK-1 receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation..... Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**."

Here we have exactly this situation, namely a ligand with affinity, but no known function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." The written description rejection is withdrawn based on the claim amendments. The double patenting rejection is maintained as the applicant has failed to address the grounds of rejection. This rejection was not made for the same reason as the 103(a) rejection, but rather the difference between CH_2 and C=O. This action is made **FINAL**.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

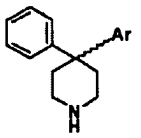
4. Claims 1-7, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevenson, Graeme I. et. al. "4,4-Disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity" *Journal of Medicinal Chemistry*, **1998**, *41*, 4623-4635, cited on the IDS, in view of Bernstein et. al. *Bioorganic and Medicinal Chemistry Letters* **2001**, *11*, 2769-2773. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

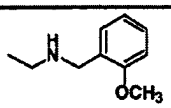
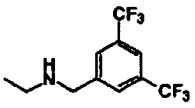
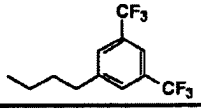
Determination of the scope and content of the prior art

(MPEP 2141.01)

Stevenson et. al. teaches compounds that are analogs of the compounds of the instant case that have the same utility. In particular the compounds on page 4630 Table 4:

Table 4. Alternative Linkers



Compound	~~~~ Ar	hNK1 IC_{50}[a]	Formula	Analysis
48		> 100[b]	$C_{20}H_{27}N_2O$	C, H, N
49		12.6 ± 8.8	$C_{21}H_{22}N_2F_6$	C, H, N
57		63 ± 7	$C_{22}H_{23}NF_6$	C, H, N*

[a] Displacement of [^{125}I]-labeled substance P from the cloned receptor expressed in CHO cells ($n = 3$). [b] 31% and 25% @ 0.1 μM. *$C_{22}H_{23}NF_6$ requires 415.1734, found 415.1750.

In order to buttress the examiner's conclusion and show that the examiner is not taking official notice, the examiner submits that Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773, clearly teaches the exact modification (down to the very precise substituents on the naphthyl ring), thus the use of naphthyl in these NK1-antagonists and the substitution of naphthyl for phenyl was very well known even in this very small field. Starting with the known selective antagonist SR48968, Bernstein modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with "over 100 aryl, heteroaryl and arylalkyl groups". In the words of Bernstein the result of this study was "the most potent, dual acting compound to

come out of this array was the naphthamide **2a**". Bernstein goes on to describe that "to follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring." It is interesting that 3-cyano-naphthyl was the preferred substituent, as in compound **4**. This 3-cyano naphthyl group is also the preferred substituent of the instant case and is what distinguishes these compounds from those of Stevenson et. al. There can be no doubt that this was the preferred substituent.

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs only in the presence of a phenyl group for the naphthyl of the instant case.

(MPEP 2141.02)

Stevenson et al. do not expressly teach the exact compounds of the instant case.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Stevenson et. al. to produce the instant invention. Analogs differing only in the substitution of phenyl for naphthyl, are *prima facie* obvious, and require no secondary teaching when the utility is the same. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine

for the chemist to replace phenyl with naphthyl especially since the chemistry developed by Stevenson was in place and the synthesis only involved using an appropriate naphthyl halide (see scheme 5 of Stevenson et. al.), moreover Stevenson suggests that lipophilicity of the aryl moiety to be important since compound **49** bearing the lipophilic CF_3 group has increased potency over compound **48** (see table 4 above), thus naphthyl being slightly more lipophilic would have increased potency. Naphthyl and more specifically, the 3-cyano naphthyl group is also the preferred substituent of Bernstein et. al. who showed the preference for naphthyl over phenyl. There can be no doubt that this was the preferred substituent.

> *Ex parte WESTFAHL*, 136 USPQ 265 (Bd. Pat. App. & Int. 1962):
>
> "Appellant relies upon the case of In re Jones, 32 CCPA 1020, 1945 C.D. 304, 579 O.G. 148, 149 F.2d 501, 65 USPQ 480 , as supporting the patentability of claim 8 because in that case a naphthyl compound was held to be patentable over the corresponding phenyl compound. However, the rejection in that case was based upon the premise, held to be untenable by the court, that benzene and naphthalene are members of a homologous series. In the present case, **the examiner does not rely upon any theory of homology but has cited a reference (Richter II) teaching that naphthalene is very similar to benzene and forms a series of analogous derivatives.**"

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 10, 12-19, 21-23 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Disclosure of the activity of the compounds and dosages that are critical or essential to the practice of the invention, but not included in the claims is not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The only information given as to what these compounds may do, at least in the pharmacological sense, is on pg. 12 of the disclosure "Individual IC50 values were reported, along with plC50. When the two IC50's obtained for a compound differed by more than 3-fold that compound was assayed one or two more times to

redetermine the value. Compounds of the present invention exhibit a Ki in the range of 1 to 100 nM in the SERT assay and have an IC50's in the range 1 to 100 nM in FLIPR assay." The applicant has given ranges of two orders of magnitude for each individual assay, without reference to a known compound that is an agonist/inhibitor and the variability in these assays make evaluation of therapeutic value difficult. For example in the case of the NK-1 receptor in transfected cells, overexpression of a GPCR can lead to many false positives in a FLIPR assay, due to high constitutive activity and the low threshold of activation. The situation is further compounded by the fact that it is possible for a single compound to be very different things at each target. In the instant case we do not know whether the compounds are partial agonists at the NK-1 receptor. It is possibly that some compounds are both SERT inhibitors and partially active at the NK-1 receptor and vice versa, or both potent inhibitors of SERT and potent antagonists at the NK-1 receptor. Applicant seems to believe these compounds are the later although no support has been provided for this assertion. Moreover, even if this dual activity was possessed by the compounds of the invention, one cannot predict a priori what the outcome of such complex pharmacological behavior would be in the complex diseases of claim 10. The article cited by the authors (Ryckmans, T., et al., B*ioorg. Med. Chem.Lett.* (2002), 12, 261). suggests that these kinds of compounds might be useful for treatement of depression and they may well be but no such evidence is provided in the instant case. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). In regard to claim 10, depression is the only

disease where such treatment might be efficacious, however this is debatable as stated in a recent review (Rosenzwieg-Lipson et. al. Pharmacology & Therapeutics 2007, 113, 134-153) pg. 140 paragraph 3 sentence 2:

> "Although the NK-1 antagonist aprepitant was not proven efficacious in Phase III depression trials (Keller et al., 2006), it is conceivable that the combination of aprepitant with an SSRI might result in rapid onset of antidepressant effects. To this end, NK-1 antagonists have been shown to potentiate the neurochemical effects of SSRIs in preclinical studies (Guiard et al., 2004). Whether this combination or other non-monoaminergic mechanisms will produce rapid onset antidepressant effects remains to be answered."

Thus the state of the art in the area of these dual antagonists is murky at best. Moreover, even if these compounds were evaluated simply as NK-1 antagonists (which it is unclear if they actually are), a recent review article (McLean, S. *Current Pharmaceutical Design* **2005**, *11*, 1529, pg. 1542 paragraph 3) states, that:

> "In summary, clinical studies with three different compounds demonstrate antidepressant efficacy in both mildly depressed as well as melancholic patients. Furthermore, the favorable side effect profile of the agents suggests a viable therapy particularly for people experiencing significant sexual side effects with currently available antidepressants. **This has to be balanced against a number of trials in which NK1 receptor antagonists failed to show activity. In addition to the previously mentioned negative trials, NKP608 another NK1 receptor antagonist was reported on the Novartis web site to have been terminated from further development for depression although it is unclear whether this was due to side effects or lack of efficacy. To date there are three positive trials in depression, one positive trial in panic, several failed trials and at least 2 negative studies."**

It seems very unlikely that one skilled in the art (a Medical Doctor or Pharmacist) would know what to do with these compounds. The real problem here is that the NK-1 receptor is a GPCR

with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor.....**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation..... Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**.

Here we have exactly this situation, namely a ligand with affinity, but no known function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility." The factors outlined in In re Wands mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to use"...."the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-7, 10, 12-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/525,303 in view of Stevenson et. al. "4,4-Disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity" *Journal of Medicinal Chemistry*, **1998**, *41*, 4623-4635, cited on the IDS.

This is a provisional obviousness-type double patenting rejection.

Copending Application No. 10/525,303 teaches compounds, compositions, and methods with compounds that are the amide analogs of the compounds of the instant case that have the same utility.

Ascertainment of the difference between the claims

It is clear that the copending application differs only in the presence of a carbonyl group for the methtylene of the instant case. Stevenson et. al. teach that the basicity of the alkyl amino nitrogen is important for the activity:

"If the 3,5-bis(trifluoromethyl)benzyloxy side chain of 12 is replaced by the 2-methoxybenzylamino group found in 1 and 2 to give 48, the resulting compound has poor affinity for the NK1 receptor (31% @ 1 íM). This is a significant departure from the observed SAR of the cis-(2S,3S)-piperidine-based series where the O- for N-substitution provided equipotent compounds (although it should be noted that 2-methoxybenzyl ether side chain in the quinuclidine type NK1 antagonist has poor NK1 affinity 26). The explanation for this may lie in the fact that in compounds such as 2 the benzylic amino group is directly attached to the piperidine/ quinuclidine ring (see above). In the case of 48 the benzylic nitrogen is not directly attached to the piperidine ring and is consequently more basic (48, pKa N-1 10.6, pKa N-2 8.2). If at physiological pH both the piperidine and side chain nitrogens protonate, the benzylic nitrogen will no longer be able to act as a hydrogen bond acceptor. A secondary factor may be that ortho substituents are not well-tolerated in this system (Table 1). To examine the effect of the pKa of the side chain nitrogen, the 3,5-bis(trifluoromethyl)benzylamino compound 49 was prepared. The inductive effect of the trifluoromethyl groups now decreases the electron density at the nitrogen (49, pKa N-1) 10.13, pKa N-2) 5.92), and it will therefore be less likely to protonate at physiological pH. This would indeed appear to be the case as 49 (IC50) 12.6 nM), although less active than 12 (IC50) 0.95 nM), did recover most of the lost affinity. Mutagenesis studies using 48 and 49 have also lent weight to this theory.24 In the case where Lys106 has been mutated to Glu106, 48 shows a large increase in NK1 affinity from >100 to 30 nM, indicating that the protonated form of 48 develops a more favorable interaction between ligand and receptor. The NK1 affinity of 49 is however decreased by this same mutation (from 8.0 to 47 nM)."

(MPEP 2141.02)

The copending application is not directed to the exact compounds of the instant case.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary that the amide analogs of the instant case would be active as suggested by Stevenson et. al.. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine

for the chemist to make the amides especially since the chemistry developed by Stevenson was in place and the synthesis only involved using an appropriate naphthyl halide or acid (see scheme 5 of Stevenson et. al.), moreover Stevenson suggests that compounds with an amino nitrogen that is too basic are less active. It goes without saying that the amino nitrogen is substantially more basic than an amide. In fact an amide is somewhat acidic.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims and those of the copending application is a clear case of double patenting.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

9. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER
2/7/08